REMARKS

Claims 1, 2-4, 10-11 and 23 remain in the application. Only Claims 1, 12 and 23 are in independent form. Reconsideration of the subject application as amended pursuant to and consistent with 37 C.F.R. §1.112 and in light of the remarks which follow are respectfully requested.

With the present response Applicants have corrected typographical errors found in the specification. Applicants enclose a set of modified pages of the description for the benefit of the Examiner.

Applicants have also corrected obvious errors found in the specification. The following clarifications are provided for the Examiner's benefit:

a) The error contained at page 4 line 24.

Point N°14 was referring to itself. This point thus obviously contains an error. Point 14 refers to a recombinant polypeptide. Point N°13 page 4 line 21 refers to a purified or isolated recombinant polypeptide comprising the amino acid sequence of secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide. By reading the specification it is obvious that point N°14 should refer to point N°13.

b) The error contained at page 20 line 26.

Page 20 line 26 relates to a polypeptide comprising an amino acid sequence having particular percentage of identity with cited amino acid sequences under which are SEQ ID N°4-6, SEQ ID N°10-12, SEQ ID N°16-17. However it refers to SEQ ID N°19 which is a DNA sequence corresponding to full length $\alpha_2\delta$-2. This paragraph thus obviously contains an error. By reading the specification it is obvious that this paragraph should refer to SEQ ID N°18. This obvious correction is further demonstrated by the reading of page 20 line 34 of the specification which mentions SEQ ID N°4-6, SEQ ID N°10-12 and SEQ ID N°16-18 as being preferred amino acids sequences of the invention.

c) The error contained at page 31 line 20 and 25.

Example 11 relates to a nucleotide sequence encoding a soluble secreted mouse $\alpha_2\delta$-3 deletion mutant of cited amino acid sequence. However it refers to SEQ ID N°25 which is a DNA sequence. This example thus obviously contains an error. By reading the specification it is obvious that this paragraph should refer to SEQ ID N°24. This obvious correction is further demonstrated by the reading of page 33 line 9-10.

In the following paragraph, Applicants first provide a summary of some of the key points of the present invention. This is followed by comments to the specific rejections set forth in the Office Action.

The invention relates to truncated $\alpha_2\delta$ calcium channel subunit cDNA sequences which encode soluble secreted polypeptides which lack a C-terminal portion of the corresponding native protein while retaining their calcium channel subunit properties.

The term "soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit" is intended to designate polypeptide sequences which, when produced by a recombinant host cell, are secreted at least partially into the culture medium rather than remaining associated with the host cell membrane (see the specification at page 8 lines 5-9).

Full length $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunits are membrane associated and thus <u>are not secreted soluble</u>. Therefore full length $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunits are not part of the invention.

Preferably the secreted soluble $\alpha_2\delta$ calcium channel subunit are human $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 polypeptides. However, due to cross species homology for the $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit, the C-terminal deletion may also be applied to other eukaryotic species.

The present application specifically discloses the following deletion mutants:

For human $\alpha_2\delta$-2:

- a 1062 amino acid long mutant (see nucleic sequence SEQ ID N°1 and amino acid sequence SEQ ID N°4)

- a 1082 amino acid long mutant (see nucleic sequence SEQ ID N°2 and amino acid sequence SEQ ID N°5)
- a 1109 amino acid long mutant (see nucleic sequence SEQ ID N°3 and amino acid sequence SEQ ID N°6).

For human $\alpha_2\delta$-3:

- a 1019 amino acid long mutant (see nucleic sequence SEQ ID N°7 and amino acid sequence SEQ ID N°10)
- a 1038 amino acid long mutant (see nucleic sequence SEQ ID N°8 and amino acid sequence SEQ ID N°11)
- a 1065 amino acid long mutant (see nucleic sequence SEQ ID N°9 and amino acid sequence SEQ ID N°12).

For human $\alpha_2\delta$-4:

- a 304 amino acid long mutant (see nucleic sequence SEQ ID N°13 and amino acid sequence SEQ ID N°16)
- a 323 amino acid long mutant (see nucleic sequence SEQ ID N°14 and amino acid sequence SEQ ID N°17)
- a 350 amino acid long mutant (see nucleic sequence SEQ ID N°15 and amino acid sequence SEQ ID N°18).

The use of some of these mutants is further illustrated through the examples referring to SEQ ID N°23 which is a truncated $\alpha_2\delta$-2 which corresponds to a 1109 amino acid long mutant to which a 6His tag has been added and the example relating to SEQ ID N°24 which is a $\alpha_2\delta$-3 deletion mutant to which a 6His tag has been added.

Claims 1, 9 and 12 stand rejected under 35 U.S.C §112, first paragraph, because the specification, while enabling for nucleotides encoding SEQ ID NO: 20 and 22, does not reasonably provide enablement for a nucleic acid encoding any other polypeptide.

The objection against Claim 9 can now be withdrawn since this claim has been deleted.

With regard to Claims 1 and 12, Applicants respectfully submit that these claims refer to secreted soluble polypeptides of $\alpha_2\delta$-2, $\alpha_2\delta$-3, $\alpha_2\delta$-4 subunit. It is to be noted that SEQ ID NO: 20 and SEQ ID NO: 22 refer to full length sequences and do not fall into the scope of Claim 1.

Truncated $\alpha_2\delta$-2, $\alpha_2\delta$-3, $\alpha_2\delta$-4 subunits have been illustrated by 3 specific sequences respectively. The one skilled in the art has enough guidance to create other deletion mutants which are secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptides which retain their voltage-dependent calcium channel properties. Experimentation will be necessary to determine the interest of using shorter or longer mutants but the skilled person has an expectation of success based on the initial guidance of the specification and hence no undue experimentation is necessary.

In view of the above, withdrawal of the rejection of Claims 1, 9 and 12 under 35 USC §112, first paragraph is respectfully requested.

Claims 2-3 and 5 stand rejected under 35 U.S.C §112, first paragraph, because the specification while being enabling for a polynucleotide encoding a substantially purified polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 20 and 22, does not reasonably provide enablement for a polynucleotide encoding a substantially purified variant having at least 90% amino acids sequence identity to SEQ ID NO 20 and 22. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

The objection against Claim 5 can now be withdrawn since this claim has been deleted.

In response, Applicants wish to point out that Claims 2 and 3 have been amended to clarify the types of amino acids substitutions which can be contemplated by the skilled person.

Amended Claim 2 is supported by the specification at page 20, line 36 to the end of page 21.

Amended Claim 3 is supported by the specification at page 20, line 36 to the end of page 21.

In view of amended Claims 2 and 3, withdrawal of the rejection of those claims under 35 USC §112, first paragraph is respectfully requested.

Claims 1, 7, 9 and 12 stand rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

The Examiner indicates that Claims 1, 9 and 12 are indefinite in that they only describe the peptide of interest by an arbitrary protein name, i.e., "alpha2delta-2" and that nothing in the claims distinctly identifies the protein.

The objection against Claim 9 can now be withdrawn since this claim has been deleted.

In response, Applicants wish to point out that protein names $\alpha_2\delta$-2, $\alpha_2\delta$-3, $\alpha_2\delta$-4 are definite, per se, for one of ordinary skill in the art. As an example, Klugbauer et.al. (The Journal of Neuroscience, January 15, 1999, 19(2): 684-691) describe two forms of the full length calcium channel $\alpha_2\delta$-2 subunit and one form of the full length calcium channel $\alpha_2\delta$-3 subunit. Thus, the wording $\alpha_2\delta$-2, $\alpha_2\delta$-3, $\alpha_2\delta$-4 provide adequate guidance as to the nature of the polypeptide which Applicants claim.

Furthermore, Applicants wish to point out that the $\alpha_2\delta$-2, $\alpha_2\delta$-3, $\alpha_2\delta$-4 subunit polypeptides of the invention are defined as mammalian secreted soluble cerebral cortical voltage-dependent calcium channel subunit polypeptides. Thus Claims 1, 9 and 12 distinctly claim the subject matter of the invention.

In view of the above, withdrawal of the rejection of Claims 1, 9 and 12 under 35 USC §112, second paragraph, is respectfully requested.

The Examiner also indicates that Claims 7 and 9 are indefinite because they recite the term "stringent conditions" which is a conditional term and because some nucleic acids which might hybridize under conditions of moderate stringency for example would fail to hybridize under conditions of high stringency.

The objection against Claims 7 and 9 can now be withdrawn since these claims have been deleted.

Claims 1, 4 and 10-12 stand rejected under 35 USC §102(b). The Examiner explains that Wei et al. disclose a human α_2 calcium channel which is 100% identical to SEQ ID NO: 1.

In response Applicants provide herewith as Exhibit 1 a sequence alignment of the human α2 calcium channel sequence disclosed in Wei et al. and SEQ ID NO: 1 disclosed in the present application.

This alignment shows that Wei et al. disclose a <u>full length</u> human $\alpha_2\delta$-2 subunit polypeptide (5463 nucleotides (AF042792)) whereas SEQ ID NO: 1 of the present application is a truncated version of this full length polypeptide (3186 nucleotides). Thus the sequence of the α2 calcium channel disclosed by Wei et al. is not the same sequence as sequence SEQ ID NO: 1. Therefore, the α2 calcium channel disclosed by Wei et al. is not 100% identical to the sequence of SEQ ID NO: 1. Furthermore it is clear from this

analysis that Wei et al. does not disclose any form of truncated calcium channel subunit. Hence Claims 1, 4, 10-12 are novel over this prior art.

The amendment of Claim 4 results from a typographical error. Appropriate sequences to be incorporated in this claim are provided at page 10, lines 16-19 of the specification as filed.

In view of the arguments set forth above withdrawal of the rejection of Claims 1, 4 and 10-12 under 35 USC §102(b) is respectfully requested.

Claims 1, 6, 7 and 9-12 are rejected under 35 USC §102(b) as being anticipated by WO9504822.

The objection against Claims 6, 7 and 9 can now be withdrawn since those claims have been deleted.

The Examiner explains that Harpold et al. disclose the cloning and expression of human voltage gated calcium channel subunits thus anticipating Claim 1.

In response, Applicants wish to draw the attention of the Examiner to the fact that Claim 1 refers to secreted soluble voltage-dependent calcium channel $\alpha_2\delta$-2, $\alpha_2\delta$-3, $\alpha_2\delta$-4 subunit polypeptides and not only to voltage gated Ca^{2+} subunits. Therefore, Harpold et al. do not disclose a purified or isolated nucleic acid encoding a mammalian secreted soluble cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide of Claim 1.

In conclusion Claim 1 is not anticipated by Harpold et al.

In view of the arguments set forth above withdrawal of the rejection of Claims 1, 6, 7 and 9 under 35 USC §102(b) is respectfully requested.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

The Commissioner is hereby authorized to charge any fees under 37.C.F.R §1.116 and 1.117 that may be required by this paper to Deposit Account No. 23-0455,

In the event the Examiner wishes to discuss any matter concerning this application, he is invited to communicate with the undersigned.

Respectfully submitted,

David R. Kurlandsky
Reg. No. 41,505
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
Tel. (734) 622-7304
Fax (734) 622-1553

Attachment - Amended claims, Version with markings to show changes made
Exhibit 1

DKIP4389.doc

"Version with markings to show changes made."

Please amend Claims 2, 3 and 4 as follows:

Claim 2 (amended). A purified or isolated nucleic acid according to claim 1, comprising a polynucleotide having at least 90% identity with the sequence encoding :

- from amino-acid 1 to between amino-acids 1027 and 1062 of SEQ ID N°20 for $\alpha_2\delta$-2,
- from amino-acid 1 to between amino-acids 984 and 1019 of SEQ ID N°22 for $\alpha_2\delta$-3

wherein the differing nucleotides encode amino acids which are the same as the amino acids of the SEQ ID N°20 and SEQ ID N°22 through codon degeneracy or encode amino acids which are equivalent to the amino acids of SEQ ID N°20 and SEQ ID N°22 either by structural homology, by net charge or hydrophobicity similarity, such that the encoded polypeptide retains its specificity and affinity properties to the biological targets of the parent polypeptides.

Claim 3 (amended). A purified or isolated nucleic acid according to claim 1, having at least 90% identity with the sequence encoding :

- from amino-acid 1 to between amino-acids 1047 and 1062 of SEQ ID N°20 for $\alpha_2\delta$-2,
- from amino-acid 1 to between amino-acids 1004 and 1019 of SEQ ID N°22 for $\alpha_2\delta$-3

wherein the differing nucleotides encode amino acids which are the same as the amino acids of the SEQ ID N°20 and SEQ ID N°22 through codon degeneracy or encode amino acids which are equivalent to the amino acids of SEQ ID N°20 and SEQ ID N°22 either by structural homology, by net charge or hydrophobicity similarity, such that the encoded polypeptide retains its specificity and affinity properties to the biological targets of the parent polypeptides.

Claim 4 (amended). A purified or isolated nucleotide sequence according to claim 1 wherein said sequence is the sequence of SEQ ID N°1, SEQ ID N°2, SEQ ID N°3, SEQ ID N°7, SEQ ID N°8, SEQ ID N°9, SEQ ID N°13, SEQ ID N°14, or SEQ ID N°15[, SEQ ID N°19 or SEQ ID N°21].

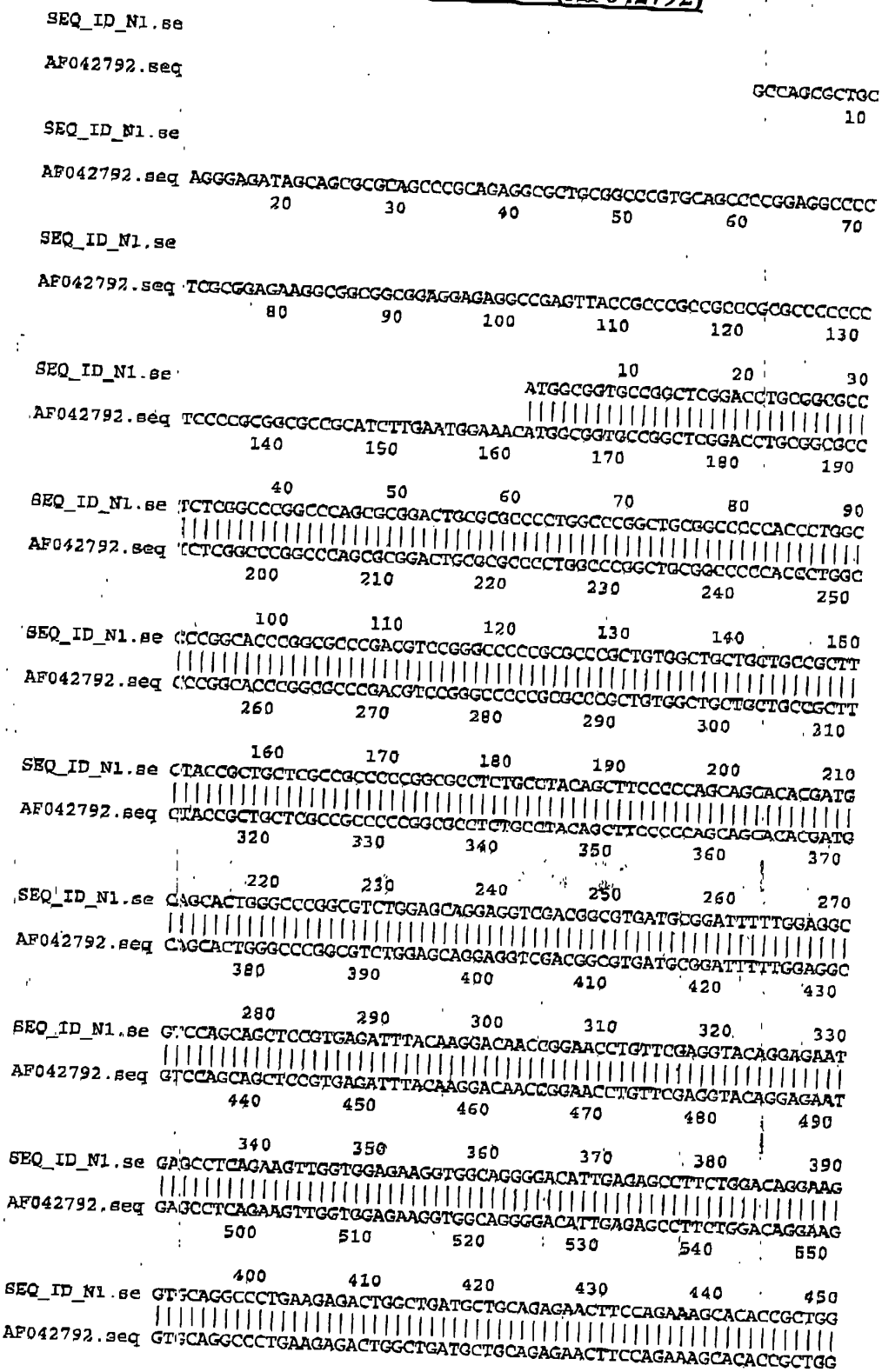
Please delete Claims 5, 6, 7 and 9.

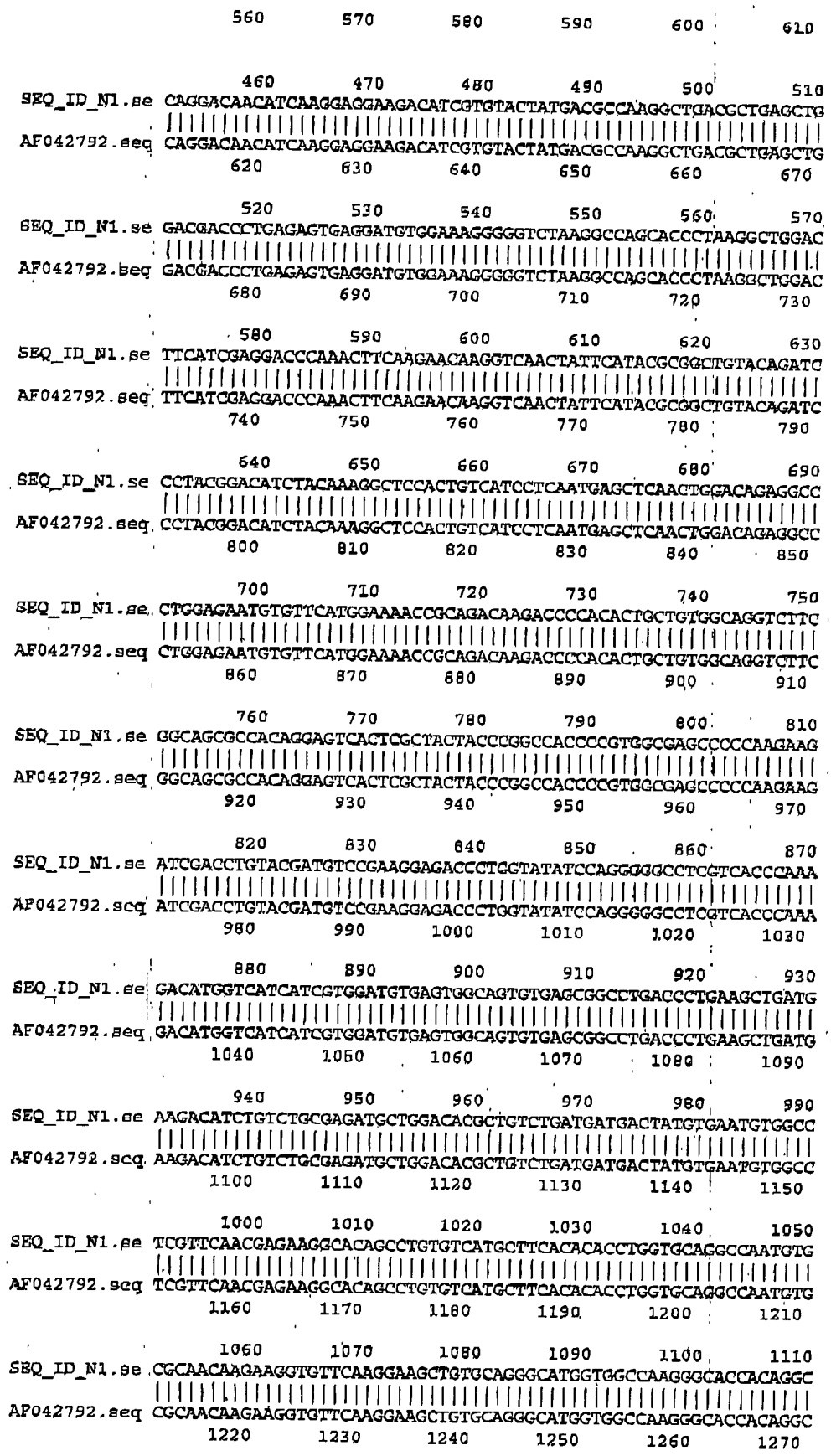
Please add new Claim 23.

Claim 23 (NEW). A purified or isolated nucleic acid having at least 90% identity with the nucleotide sequence of SEQ ID N°1, SEQ ID N°2, SEQ ID N°3, SEQ ID N°7, SEQ ID N°8, SEQ ID N°9, SEQ ID N°13, SEQ ID N°14, or SEQ ID N°15.

Exhibit 1

Sequence alignement of sequence SEQ ID N°1 of the patent application and the sequence of the human alpha 2 calcium channel disclosed by Wei et al. (AF042792)

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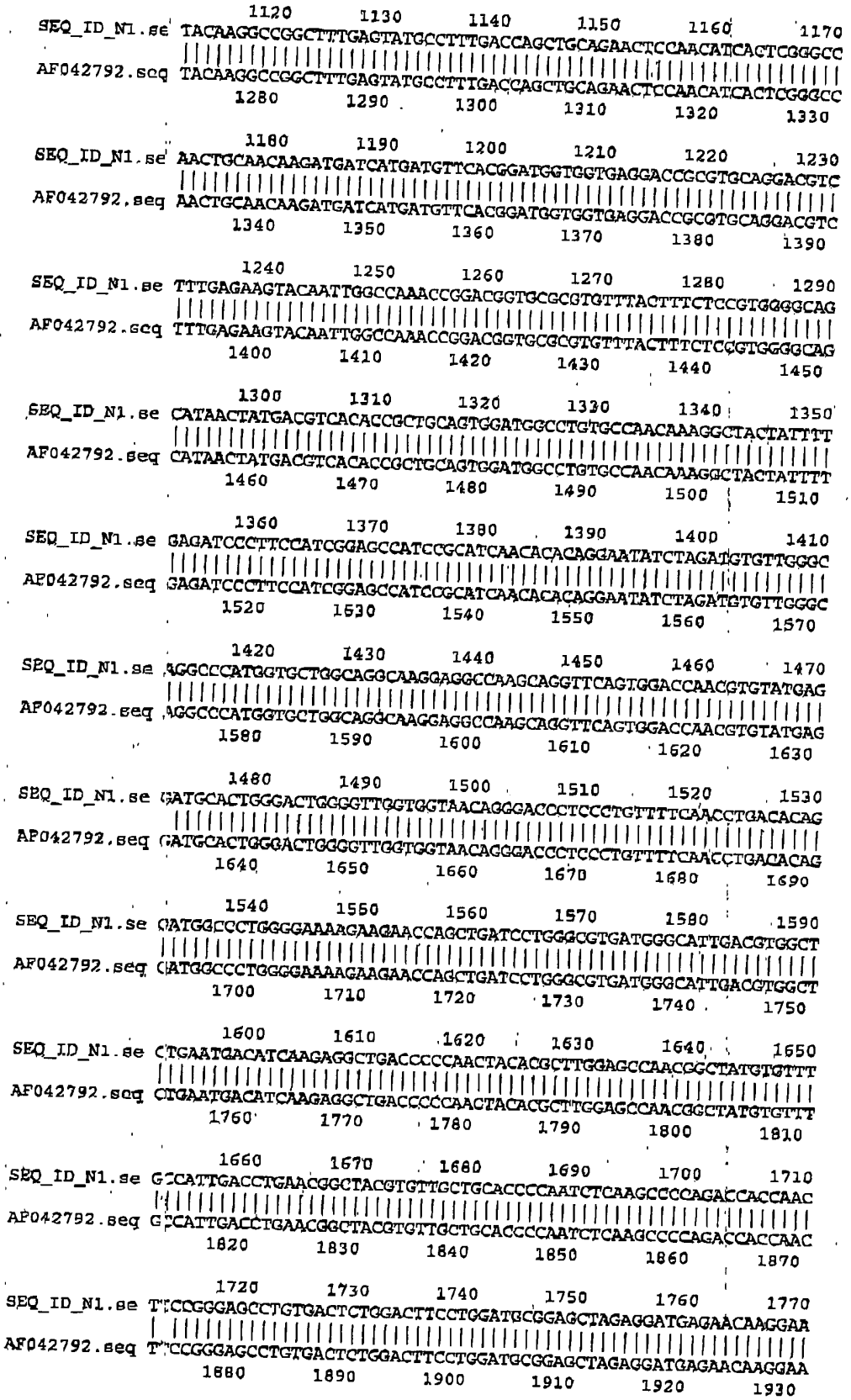
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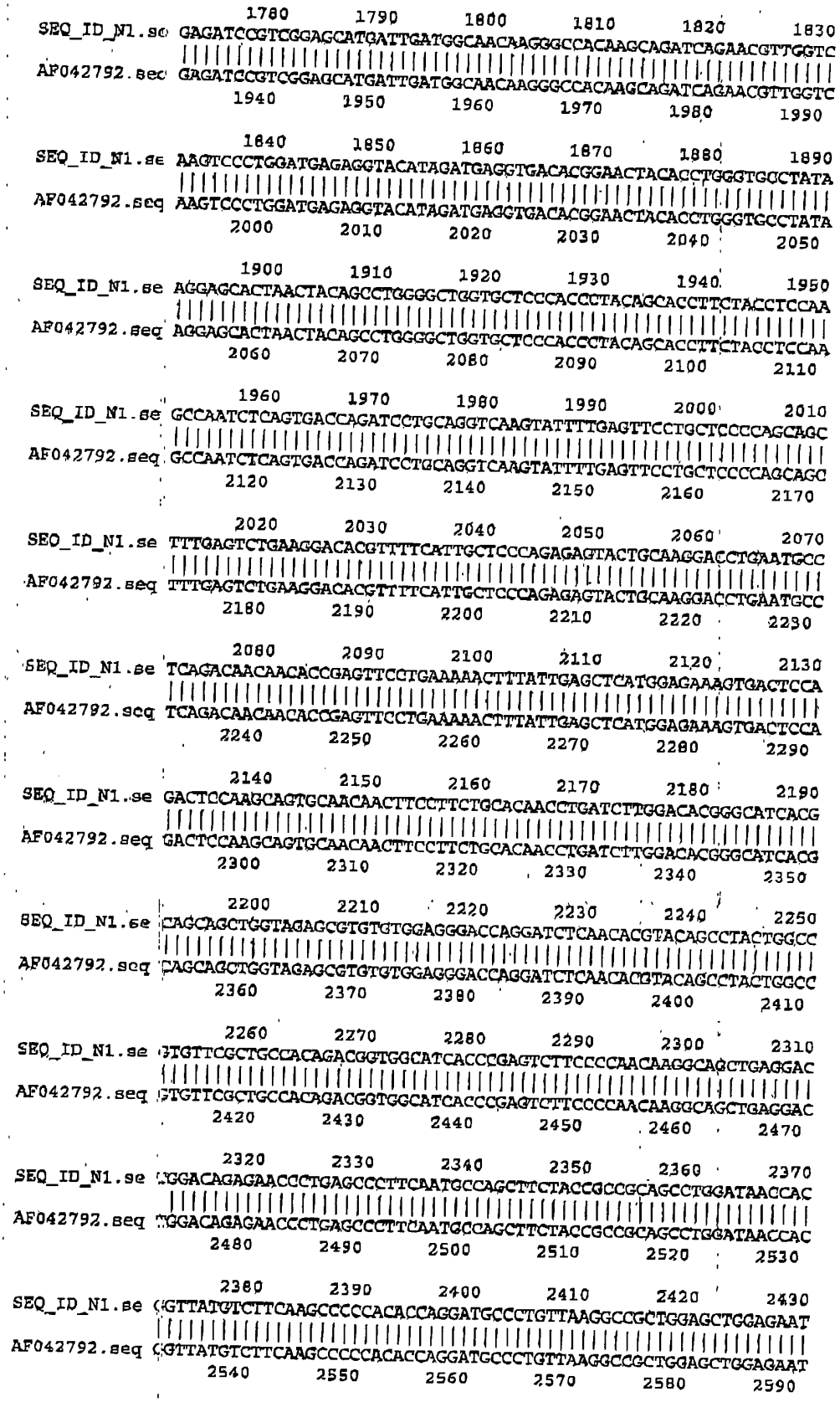
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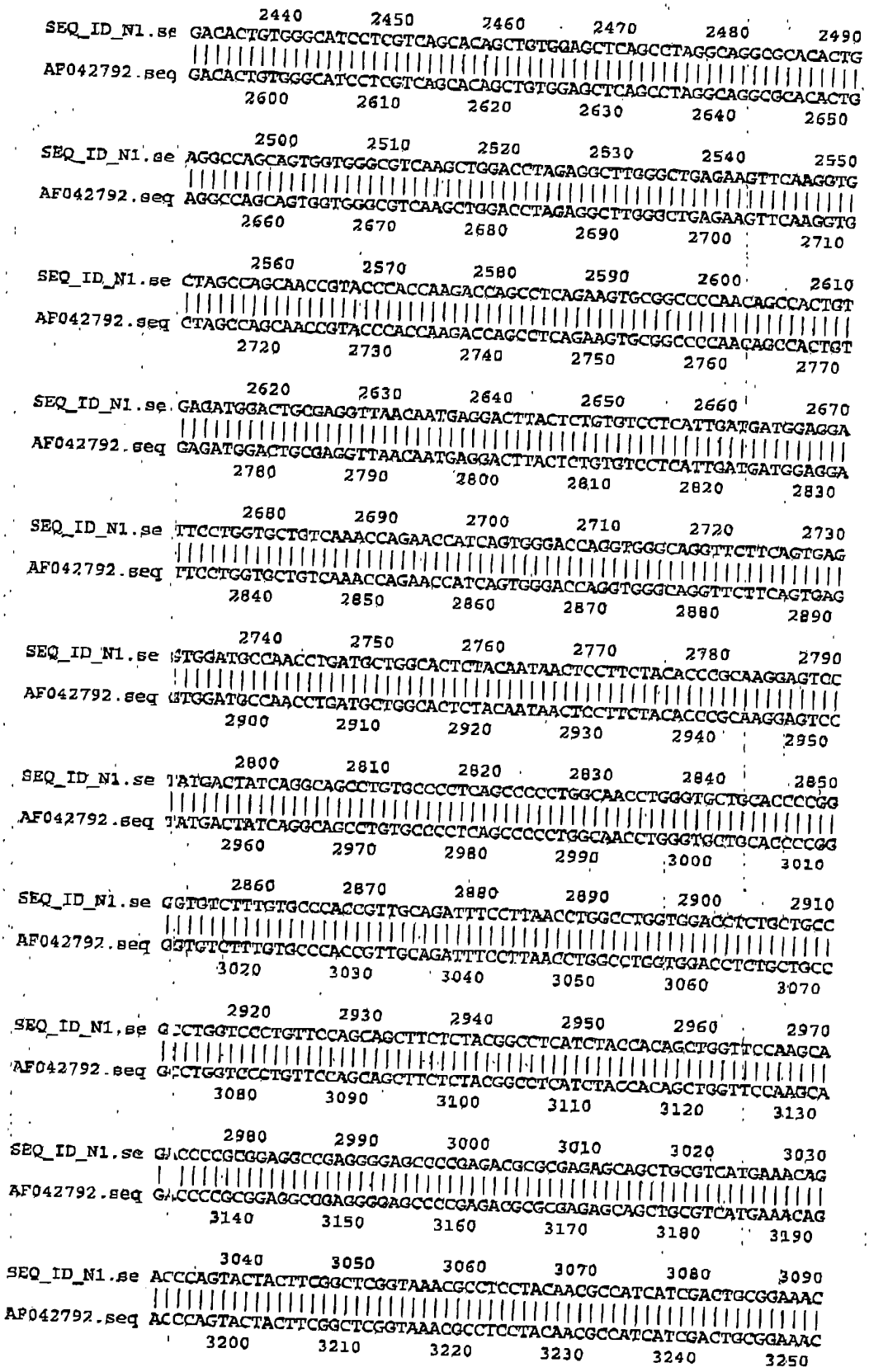
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SEQ_ID_N1.se

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